rationale of therapy. The turnover time in the production of normal epidermis is 28 days. The turnover time in psoriasis is three to four days. This accounts for the dramatic growth and thickening of the skin.

Methyltrexate, an antimetabolic dioxyribonucleic acid (DNA) inhibitor used effectively in the treatment of choriocarcinoma was found to be very effective in the treatment of psoriasis. This is an exceedingly potent and dangerous chemotherapeutic agent, the use of which can be justified only in severe cases of generalized psoriasis. Its use should be limited to oncologists or dermatologists familiar with the agent and capable of closely monitoring changes in the liver, bone marrow and kidneys. The benefit-to-risk ratio is unfavorable except in very unusual cases.

A new method of treatment used by several investigators appears very promising. Historically it was noted that in travelers afflicted with psoriasis there was an especially beneficial effect when they visited the region of the Dead Sea. It was reasoned that the good results may have accrued from the type of light penetrating the extra thickness of the atmosphere. Indeed, there was found to be a longer wave length in the ultraviolet spectrum, the shorter wave length having been filtered out. It was observed that certain chemicals (psoralens) used in the treatment of viteligo in India and Egypt as long ago as 2,000 years, also had a beneficial effect on psoriasis in some instances.

The combined use of the longwave (UV-A 320 to 400 nm) light and methoxsalen (8 methoxypsoralen) or trioxsalen (4, 5′, 8 trimethyl-psoralen) produced remission of the psoriatic lesions. Methoxsalen, the more commonly used psoralen increases photosensitivity in the skin and increased pigmentation in the presence of ultraviolet light. The photo-excited psoralen molecules bind to the DNA molecule in a manner to inhibit its replication. This effect is most pronounced in the presence of longwave UV-A (320 to 400 nm). The shortwave UV-B (275 to 320 nm) is relatively ineffective. The most effective use of methoxsalen is by oral administration. Topical use is unsatisfactory because of difficulty in controlling dosage. Severe cases of photosensitivity often result in blistering and irregular disfiguring hyperpigmentation of the skin. Topically and intraperitoneally, methoxsalen and longwave or conventional ultraviolet light have produced squamous cell carcinoma in animal studies.

Methoxsalen administered orally has not been shown to potentiate carcinogenesis or hepatotoxicity in human subjects in a study extending over 20 years. Methoxsalen, therefore, appears to be a safe drug, which, if administration is followed by exposure to longwave UV-A (320 to 400 nm), is effective in causing the remisison of psoriatic lesions. Careful dosage and careful exposure of measured amounts of irradiation are essential to the success of this method of treatment.

JAMES E. ANHALT SR, MD

REFERENCES

Harber LC: Editorial: Photochemotherapy of psoriasis. N Engl J Med 291:1251-1252, Dec 5, 1974

Swanbeck G, Thyresson-Hok M, Bredberg A, et al: Treatment of psoriasis with oral psoralens and longwave ultraviolet light—Therapeutic results and cytogenetic hazards. Acta Derm Venereol 55:367-376, 1975

Nonsteroid Anti-inflammatory Agent for Treatment of Rheumatoid Arthritis

AMONG A NUMBER of new agents recently placed on the market for treatment of arthritis, tolmetin sodium (Tolectin®) possesses anti-inflammatory analgesic and antipyretic activity. While the exact mechanism of action is unknown, this new nonsteroidal anti-inflammatory drug is useful as an adjunct to the treatment of rheumatoid arthritis, particularly in patients who are sensitive to aspirin. This medication comes in a dosage strength of 200 mg and the recommended dose is 1,200 to 2,000 mg a day in divided doses taken with food to avoid gastric irritation that can be a problem with this drug. Double-blind cross-over studies have been made and findings indicate that in recommended doses tolmetin is as effective as aspirin and indomethacin. Tolmetin sodium is indicated for the relief of signs and symptoms of rheumatoid arthritis in acute flare-ups and also in long-term management of the chronic disease.

Guidelines for gauging improvement with use of this medication have been a reduction in swelling and pain, a reduction of the number of involved joints, a reduction of the duration of morning stiffness, or a decrease in disease activity and improved functional capacity. While this drug has been noted to be equal to indomethacin and aspirin in controlling disease activity, the frequency of gastrointestinal adverse effects and tinnitus was definitely less than those of patients treated with aspirin, and the incidence of central nervous system adverse effects was less than with the indomethacin treated patients.

Contraindications to this medication are a direct sensitivity to the medication and a possible cross-sensitivity to other nonsteroidal inflammatory drugs. Caution should be observed in any patient with gastrointestinal symptoms and a past history of peptic ulcer or gastrointestinal bleeding, and this should be a reason for withdrawal of medication. There has been some fluid retention with the use of tolmetin sodium. The metabolites of this drug have been found to give a positive test for proteinuria utilizing sulfasalicylic acid, with no interference in tests for this urinary constituent using dye-impregnated commercial strips, or urine sticks. Use of this medication during pregnancy and in nursing mothers is not advised. The drug interactions have been few even though tolmetin sodium does extensively bind to plasma protein.

This drug can be used in conjunction with other treatments. Conjoint use with acetaminophen, gold, and steroids has been carried out. It is suggested that tolmetin sodium is an adjunct for the treatment of severe cases of rheumatoid arthritis. Studies also have indicated that in a number of patients there was an effective response to this medication. These responses cannot be predicted before its use; therefore, tolmetin sodium may be used if a substitute or an adjunct to therapy in patients with severe rheumatoid arthritis is needed.

RICHARD C. BARNETT, MD

REFERENCES

Bain LS, el-Ghobarey AF, Collins RM, et al: Tolmetin: An evaluation of a new preparation in the treatment of rheumatoid arthritis. Br J Clin Pract 29:208-210, Aug 1975

Aylward M, Maddock J, Parker RJ, et al: Evaluation of tolmetin in the treatment of arthritis: Open and controlled double-blind studies. Curr Med Res Opin 4:158-169, 1976

Ward JR (Ed): Tolmetin: A New Non-steroidal Anti-inflammatory Agent—Proceedings of a Symposium, Washington, DC, Apr 5-6, 1975 (International Congress Series #372). Amsterdam, The Netherlands and New York, NY, Excerpta Medica, 1975

Newer Nonsteroidal Anti-Inflammatory Compounds

FEW ARTHRITIC PATIENTS can be cured, but most who suffer from the arthritides need not become prostrate cripples. Unfortunately, the key element that sets off the chain of events leading to synovitis is unknown. Until there is a better understanding of what triggers the disease, physicians cannot hope to intervene much earlier, and must be content with small improvements in treatment.

Family physicians, therefore, are put in the position of attempting to estimate minor benefits of new anti-inflammatory drugs. However, even small degrees of improvement are welcomed by patients.

The most common drugs now available to family physicians are nonsteroidal anti-inflammatory agents such as talmetin, naproxin, fenaprofin calcium and ibuprofin. These drugs do add depth to the arthritis armamentarium. They all appear to be as effective as aspirin, but have fewer harmful side effects.

Naproxin (Naprosyn®) is an arylalkanoic acid derivative that has considerable promise in the treatment of arthritis. It has been widely tested in clinical trials. In the dosage of 250 mg twice a day it is comparable to aspirin and indomethacin but is tolerated better than either of these agents. Combination therapy using naproxin has been shown to be more effective than aspirin alone.

The mode of action of ibuprofin (Motrin®) in inflammation is unknown. It is an analgesic with nonsteroidal anti-inflammatory activity. It has been shown to have a suppressive mechanism of action on mediators of inflammation (such as decreasing prostaglandin synthesis) similar to indomethacin. One paper reports ketoprofin to be better tolerated than ibuprofin and at least as efficacious. Ibuprofin's significant anti-inflammatory activity appears to be effective only in the upper end of the range of 900 to 2,400 mg per day. Antiarthritic activity of the drug in lower dosages probably reflects a primary analgesic and perhaps an antipyretic effect rather than suppression of inflammation.

Fenoprofin calcium (Nalfon®) is another proprionic acid derivative, but its safety and effectiveness have not been established in rheumatic arthritic patients who are designated by the American Rheumatism Association as Functional Class IV (largely or wholly incapacitated with the patient bedridden or confined to a wheelchair permitting little or no self-care).

Talmetin (Tolectin®) is an effective and safe anti-inflammatory agent. In addition, it appears to be less toxic to the liver than even aspirin. In the case of juvenile rheumatoid arthritis, results of liver function tests improved during its administration and, again, it appeared to be as effective as aspirin in the short-term management of juvenile rheumatoid arthritis.

Scientific literature on arthritis practically ignores the recent excitement over hormonal therapy of rheumatoid arthritis. High blood levels of estro-